Impact of renal function on coronary plaque composition

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Abstract

Introduction

Background. Recent studies have demonstrated that patients with chronic kidney disease are at high risk of atherosclerosis. Recently it has been found that coronary plaque components can be evaluated by integrated backscatter intravascular ultrasound (IB-IVUS), and lipid-rich plaque is associated with vulnerable plaque. The aim of the study was to investigate the relationship between renal function and tissue characterization of coronary plaque composition at the target stenotic site for percutaneous coronary intervention (PCI).

Methods. We prospectively performed IB-IVUS before elective PCI in 89 consecutive patients with stable angina. According to estimated glomerular filtration rate (eGFR), they were divided into two groups (eGFR <60 ml/min/1.73 m² or eGFR ≥60 ml/min/1.73 m²). The tissue characteristics of the coronary plaque at each target stenotic site were evaluated by three-dimensional (3D) IB-IVUS just before PCI procedure.

Results. The patients with eGFR <60 ml/min/1.73 m² had higher percentage of lipid volume and lower percentage of fibrous volume compared to the patients with eGFR ≥60 ml/min/1.73 m² on the 3D IB-IVUS images (36.7 ± 10.6% versus 28.7 ± 9.3%, P < 0.001 and 59.1 ± 8.7% versus 66.3 ± 8.3%, P < 0.001, respectively). eGFR showed a significant negative correlation with lipid volume and had a significant positive correlation with fibrous volume in coronary plaques (r = −0.44, P < 0.0001, and r = 0.46, P < 0.0001, respectively).

Conclusions. Impaired renal function was related to higher percentage of lipid volume and lower percentage of fibrous volume in coronary plaque. Our findings may explain the increasing risk of cardiovascular events in patients with renal dysfunction.

Keywords: chronic kidney disease; coronary heart disease; integrated backscatter intravascular ultrasound; percutaneous coronary intervention; renal function

Materials and methods

Study population

This study consisted of patients with stable angina pectoris who were treated with their first PCI for coronary lesions with severe stenosis.
Confounding (age and gender) and various factors that might be related to renal function and ultrasound parameters. We performed the multiple regression analysis adjusting for these factors.

QCA and IVUS analysis

For all patients, 100–200 mg doses of aspirin were administered daily for at least 14 days before PCI procedures. Just before PCI procedures, a bolus of 7000–10 000 U heparin was administered from arterial sheath. Intracoronary infusion of 2.5–5 mg isosorbide dinitrate was used before angiography for QCA and IVUS.

Coronary angiograms were obtained before PCI. The projection showing the maximal degree of stenosis (worst view) was selected for QCA. QCA analysis was analysed using a contour detection minimum cost algorithm (QCA-CMS Version 3.0, MEDIS, Leiden, The Netherlands) as previously described [17].

Commercially available imaging systems (Clear View, Boston Scientific, Natick, Massachusetts, for imaging, and SCIMED, Freemont, California, for a motored pull-back device and a commercial scanner) were used for conventional IVUS analysis. In accordance to the guidelines [22], the external elastic membrane (EEM) and lumen were traced by manual planimetry. The cross-sectional area (CSA) of the EEM was measured by tracing the leading edge of the intima. Plaque plus media (P&M) CSA was calculated as EEM – lumen CSA. The percent plaque area was defined as: (lumen area – lumen area/EEM area) × 100. The lesion length was also determined by IVUS measurement. The lumen area of 4.0 mm² in both sides of minimum luminal area was measured, and the length between the proximal and distal points was defined as the lesion length. Conventional three-dimensional (3D) IVUS image analysis was performed to compute the vessel volume, lumen volume and total plaque volume (sum of EEM, lumen CSA, P&M CSA at 1-mm axial intervals for the analysis segments).

IB signals were obtained with a commercially available system connected to the IVUS imaging system (IB-IVUS, YD Co., Ltd, Nara, Japan). The IB value for each tissue component was calculated as an average power of the ultrasound backscattered signal from a small volume of tissue using a fast Fourier transform, measured in decibels (dB). The definition of the IB value was determined for each of three histologic categories: fibrous area, lipid area and high signal area (a part of the calcification on the inner surface). The percentage of fibrous volume (fibrous volume/plaque volume) and that of lipid volume (lipid volume/plaque volume) and high signal volume (high signal volume/plaque volume) was automatically calculated, respectively. The analysis for 3D IVUS images including lipid volume, fibrous volume, and high signal volume were calculated with the sum of fibrous, lipid and high signal area in each CSA at 1-mm axis intervals, respectively (Figure 1).

Statistical analysis

All statistical analyses were performed using SPSS (SPSS, Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation values and compared using Student’s t-test. A simple regression analysis was used to test the relationship between renal function and ultrasound parameters. We performed the multiple regression analysis adjusting for confounding (age and gender) and various factors that might be related to lesion characteristics (hypertension, diabetes, treatment with chronic statin administration, and smoking status). A P-value of < 0.05 was considered significant.

Results

We tried to perform IVUS just before PCI for 95 patients. However, IVUS catheter was not crossed to the target lesion in six patients. Therefore, we analysed 89 patients. Of them, 39 patients had eGFR < 60 ml/min/1.73 m² and 50 had eGFR ≥ 60 ml/min/1.73 m². During the study period, four patients with eGFR < 30 ml/min/1.73 m² underwent PCI. However, IVUS catheter was crossed to none of them. Therefore, all patients had eGFR ≥ 30 ml/min/1.73 m². A total of 30 randomly selected lesions were measured for evaluation of inter- and intra-observer agreement. The inter- and intra-observer variabilities of lipid volume and fibrous volume in 3D IVUS images were well correlated (r = 0.96 [P < 0.001] and r = 0.96 [P < 0.001], and r = 0.94 [P < 0.001] and r = 0.93 [P < 0.001], respectively).

Table 1 shows the clinical characteristics of the enrolled patients. The mean age was 67 ± 10 years of age. Of enrolled subjects, 84 were males, 73 had hypertension and 25 were current smokers. The mean body mass index was 24 ± 3.2 kg/m². The mean eGFR was 63 ± 15 ml/min/1.73 m². Of 89 included patients, 39 received long-term statin treatment for > 6 months before PCI and 50 patients did not receive statin therapy before PCI at all. There were significant differences in age and incidence of hypertension between the two groups. However, other risk factors and lipid profile were similar between the two groups.

Table 2 gives the angiographical findings, QCA and IVUS data. There were no significant differences in the culprit lesion and lesion characteristics between the two groups. The reference diameter (2.61 ± 0.60 mm versus 2.42 ± 0.48 mm, P = 0.1), minimum lumen diameter (0.72 ± 0.23 mm versus 0.69 ± 0.24 mm, P = 0.6), percent diameter stenosis (72 ± 9% versus 71 ± 8%, P = 0.6) and lesion length (10.9 ± 3.5 mm versus 10.4 ± 4.5 mm, P = 0.5) were also comparable. As to the conventional IVUS data, various parameters were similar between the two groups. The lumen area were 2.1 ± 0.8 mm² in the group with eGFR < 60 ml/min/1.73 m² and 2.1 ± 0.8 mm² in the group with eGFR ≥ 60 ml/min/1.73 m². However, in the two-dimensional IB-IVUS assessment, the percent lipid area was greater and the percent fibrous area was smaller at the most severe stenotic site in the group with eGFR < 60 ml/min/1.73 m² than in the group with eGFR ≥ 60 ml/min/1.73 m², but those were not statistically significant. On the other hand, patients with eGFR < 60 ml/min/1.73 m² had a significantly greater percent lipid volume and a significantly smaller percent fibrous volume compared to patients with eGFR ≥ 60 ml/min/1.73 m² on the 3D IB-IVUS images (36.7 ± 10.6% versus 28.7 ± 9.3%, P < 0.001 and 59.1 ± 8.7% versus 66.3 ± 8.3%, P < 0.001, respectively) (Figure 2).

A linear regression analysis showed that eGFR had a significant negative correlation with lipid volume and had a significant correlation with positive fibrous volume in coronary plaques (r = −0.44, P < 0.001, and r = 0.46, P < 0.001, respectively) (Figure 3). On multivariate
Fig. 1. Representative images of serial conventional intravascular ultrasound and integrated backscatter intravascular images in patients with eGFR < 60 ml/min/1.73 m² (A) or with eGFR ≥ 60 ml/min/1.73 m² (B). The percentage of lipid volume and the percentage of fibrous volume were 46.5% and 51.5% in (A), and 29.9% and 68.4% in (B), respectively. Blue = lipid pool; green yellow = fibrous lesion; red = high signal lesion.

Fig. 2. Volumetric plaque analysis using integrated backscatter intravascular ultrasound. (A) Lipid volume (patients with eGFR < 60 ml/min/1.73 m²: 36.7 ± 10.6%, patients with eGFR ≥ 60 ml/min/1.73 m²: 28.7 ± 9.3%, P < 0.001). (B) Fibrous volume (patients with eGFR < 60 ml/min/1.73 m²: 59.1 ± 8.7%, patients with eGFR ≥ 60 ml/min/1.73 m²: 66.3 ± 8.3%, P < 0.001).
Diabetes, n (%) 65 (73) 31 (80) 34 (68) 0.2
Smoker, n (%) 22 (25) 6 (15) 16 (33) 0.08

Table 2. Data on quantitative coronary angiography and intravascular ultrasound

<table>
<thead>
<tr>
<th>Variable</th>
<th>eGFR &lt; 60 ml/min/1.73 m²</th>
<th>eGFR ≥ 60 ml/min/1.73 m²</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>QCA</td>
<td></td>
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<tr>
<td>Reference vessel diameter (mm)</td>
<td>2.61 ± 0.60</td>
<td>2.42 ± 0.48</td>
<td>0.1</td>
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<tr>
<td>Minimum lumen diameter (mm)</td>
<td>0.72 ± 0.23</td>
<td>0.69 ± 0.24</td>
<td>0.6</td>
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<tr>
<td>Diameter stenosis (%)</td>
<td>72 ± 9</td>
<td>71 ± 8</td>
<td>0.6</td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>10.9 ± 3.5</td>
<td>10.4 ± 4.5</td>
<td>0.5</td>
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<tr>
<td>Conventional IVUS</td>
<td></td>
<td></td>
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<tr>
<td>External elastic membrane area (mm²)</td>
<td>11.1 ± 3.2</td>
<td>10.0 ± 3.1</td>
<td>0.1</td>
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<tr>
<td>Plaque area (mm²)</td>
<td>8.9 ± 3.0</td>
<td>7.9 ± 2.9</td>
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<tr>
<td>Percent plaque area (%)</td>
<td>79 ± 7</td>
<td>78 ± 7</td>
<td>0.6</td>
</tr>
<tr>
<td>Percent plaque volume (%)</td>
<td>130 ± 82</td>
<td>108 ± 61</td>
<td>0.1</td>
</tr>
<tr>
<td>Percent plaque volume (%)</td>
<td>64 ± 8</td>
<td>61 ± 9</td>
<td>0.1</td>
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<tr>
<td>IB-IVUS</td>
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<tr>
<td>Lipid area (%)</td>
<td>36 ± 12</td>
<td>31 ± 11</td>
<td>0.08</td>
</tr>
<tr>
<td>Fibrous area (%)</td>
<td>60 ± 11</td>
<td>64 ± 10</td>
<td>0.07</td>
</tr>
<tr>
<td>High signal area (%)</td>
<td>4.2 ± 3.1</td>
<td>4.5 ± 3.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Lipid volume (%)</td>
<td>37 ± 11</td>
<td>29 ± 9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrous volume (%)</td>
<td>59 ± 9</td>
<td>66 ± 8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High signal volume (%)</td>
<td>4 ± 3</td>
<td>5 ± 3</td>
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Table 3. Multiple linear regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression coefficient</th>
<th>Beta-coefficient</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent lipid volume</td>
<td>0.21</td>
<td>0.19</td>
<td>0.05</td>
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<td>Male gender</td>
<td>5.89</td>
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<td>Hypertension</td>
<td>−1.8</td>
<td>−0.08</td>
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</tr>
<tr>
<td>Diabetes</td>
<td>1.55</td>
<td>0.07</td>
<td>0.4</td>
</tr>
<tr>
<td>Smoker</td>
<td>2.06</td>
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<td>0.4</td>
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<tr>
<td>Statin administration</td>
<td>−4.80</td>
<td>−0.22</td>
<td>0.02</td>
</tr>
<tr>
<td>Percent fibrous volume</td>
<td>−0.38</td>
<td>−0.53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>0.19</td>
<td>0.21</td>
<td>0.03</td>
</tr>
<tr>
<td>Male gender</td>
<td>−5.06</td>
<td>−0.13</td>
<td>0.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.79</td>
<td>0.04</td>
<td>0.7</td>
</tr>
<tr>
<td>Diabetes</td>
<td>−1.38</td>
<td>−0.08</td>
<td>0.4</td>
</tr>
<tr>
<td>Smoking</td>
<td>−2.18</td>
<td>−0.10</td>
<td>0.3</td>
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<tr>
<td>Statin administration</td>
<td>4.57</td>
<td>0.25</td>
<td>0.01</td>
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<tr>
<td>eGFR</td>
<td>0.34</td>
<td>0.55</td>
<td>&lt;0.001</td>
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</table>

Percent fibrous volume in coronary plaques (β = −0.53, P < 0.001, and β = 0.55, P < 0.001, respectively) (Table 3).

We performed sub-analysis with reference to treatment with statin prior to PCI. In the group with eGFR ≥ 60 ml/min/1.73 m², the percent lipid volume was 25.8% with statin and 30.7% without statin (P = 0.004). The percent fibrous volume was 69.0% with statin and 64.3% without statin (P = 0.035). On the other hand, in the group with eGFR < 60 ml/min/1.73 m², the percent lipid volume was 33.2% with statin and 44.0% without statin (P = 0.047). The percent fibrous volume was 62.2% with statin and 56.1% without statin (P = 0.030).

linear regression analysis after adjustment for confounding factors, eGFR had a significant negative correlation with lipid volume and had a positive significant correlation with fibrous volume in coronary plaques (β = −0.53, P < 0.001, and β = 0.55, P < 0.001, respectively) (Table 3).

QCA = quantitative coronary angiography; IVUS = intravascular ultrasound; IB-IVUS = integrated backscatter IVUS.
Discussion

In the present study, we showed that a lower eGFR was associated with a component of more lipid and less fibrous volume in the severe coronary lesions, although angiographic data on QCA and conventional IVUS data including the EEM area and percent plaque area were similar between patients with impaired renal function and those with preserved renal function. Furthermore, a lower eGFR was strongly predictable for lipid-rich composition in coronary plaque even after the multivariate regression analysis among other coronary risk factors.

Previous reports have suggested that metabolic syndrome or high insulin levels could predict lipid-rich plaque analysed by IB-IVUS [17,18]. There is an association between inflammatory status and plaque characteristics [23]. Chronic uraemia, anemia and/or coronary risk factors including impaired glucose tolerance, diabetes, hypertension and dyslipidaemia are frequently seen in patients with renal dysfunction [24]. Furthermore, increased levels of homocysteine and inflammatory markers are common in such a population [25]. Therefore, our data might not be so surprising. However, until now, there have been limited reports regarding the relationship between renal function and coronary plaque components. Conventional IVUS studies suggest that coronary plaque growth is not accelerated in patients with chronic renal insufficiency [13,14]. Similar findings have been also reported in carotid plaque [26]. Thus, there has been poor understanding of the underlying mechanisms by which rates of cardiovascular events are very high in patients with kidney disease. Unique characteristics of plaque composition in patients with renal dysfunction were seen in our present study. Our findings might explain why patients with chronic kidney disease have an increasing risk of cardiovascular events, especially acute coronary syndrome.

IB-IVUS is a sensitive tool to detect coronary components. It is difficult to characterize the composition of coronary plaques and to identify vulnerable plaques by grey-scale conventional IVUS. On the other hand, it has been reported that colour-coded tissue maps of plaque components detected by IB-IVUS have a fine correlation with histological and angiographic findings [15]. Recent studies suggest that plaques of culprit lesions in patients with myocardial infarction are not necessarily those with severe stenosis but are often highly inflammatory vulnerable plaques with mild-to-moderate stenosis [27,28]. Large lipid cores are considered to be histologic markers for plaque vulnerability which is directly related to a risk of plaque rupture [29,30]. Sano and co-workers have suggested that vulnerable plaque and stable plaque as classified by IB-IVUS are useful in predicting acute coronary syndrome [16]. We previously reported that a high-lipid core area measured by IB-IVUS predicts procedure-related complications including occurrence of myocardial infarction in elective PCI with stent implantation [31]. Therefore, it is very important to detect plaques containing more lipid and less fibrous tissue. In patients with renal dysfunction, pharmacological intervention and/or distal protection device in addition to PCI might be useful to decrease periprocedural complications.

Kawasaki and co-workers showed that medical therapy such as statins reduced the lipid volume [32]. We previously reported that lipid-rich coronary plaques at severe stenotic sites are prevented in patients who received chronic statin treatment [19]. Studies suggest that statin treatment is effective in reducing cardiovascular events in patients with chronic kidney disease [33,34]. In the present study, statin treatment had a beneficial effect on reducing lipid volume in patients with eGFR < 60 ml/min/1.73 m². However, there was no patient with eGFR < 30 ml/min/1.73 m² in the present study, and further investigation is needed in this context.

This study has some limitations. Firstly, a relatively small number of patients in a single centre were enrolled into the study. Furthermore, patients with acute coronary syndrome were excluded. Secondly, unexpectedly, patients
with eGFR < 30 ml/min/1.73 m² including haemodialysis were not enrolled. During the study period, four patients with eGFR < 30 ml/min/1.73 m² underwent PCI; however, we could not cross IVUS catheter to them. Therefore, we could not evaluate IVUS analysis in patients with most severe renal dysfunction. Thirdly, the debulking of the surface of coronary artery may occur during a simple passage of the IVUS catheter. These factors might affect the results. Fourthly, data on cardiovascular events after PCI must be collected in the future observation, because these data might have a great clinical importance.

In conclusion, we demonstrated that patients with impaired renal function have markedly higher lipid volume and lower fibrous volume in coronary plaque detected by IB-IVUS. Our findings could explain the increasing risk of cardiovascular events in such patients. Thus, more careful attention should be paid to those patients.

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Conflict of interest statement. None declared.

References

31. Utani T, Amano T, Ando H et al. The Correlation between lipid volume in the target lesion, measured by integrated backscatter
Prevalence of chronic kidney disease in patients with suspected sleep apnoea

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Abstract

Background. Little is known about the epidemiology of chronic kidney disease (CKD) in patients with suspected sleep apnoea (SA).

Methods. Glomerular filtration rate (eGFR) was calculated in consecutive patients referred for full-night observed in-hospital polysomnography. SA was defined as the respiratory disturbance index (RDI) > 5.

Results. One hundred and fifty-eight patients were studied. The age (mean ± SD) was 61.2 ± 12.7 years, body mass index 29.5 ± 5.9 kg/m² and eGFR 86.1 ± 21.7 mL/min/1.73 m². SA was present in 133 patients (85%). The eGFR was 94.6 7 mL/min/1.73 m² in patients without SA and 84.5 7 mL/min/1.73 m² in patients with SA [mean difference (95% confidence interval) 10.0 (0.6–19.4) mL/min/1.73 m²; P = 0.037]. Seventy patients had eGFR ≥ 90 mL/min/1.73 m² (group 1), and 70 patients had between 60 and 89 mL/min/1.73 m² (group 2), and 18 patients had 30–59 mL/min/1.73 m² (CKD 3). Although the prevalence of SA did not differ among the groups (group 1: 80%; group 2: 86%; CKD 3: 94%), the number of central sleep apnoeas (CSA) per hour was 5.9 ± 12.2 in CKD 3, six times greater compared to patients with eGFR ≥ 60 mL/min/1.73 m² (1.0 ± ± 2.1; P = 0.01). The prevalence of obstructive SA did not differ between the groups. After adjustment for age, gender, BMI, hypertension, diabetes mellitus and smoking status, CKD 3 (P = 0.0004) and New York Heart Association class ≥ 3 (P = 0.0001) remained predictive of CSA events per hour.

Conclusions. eGFR is reduced in patients with SA, particularly in those with episodes of CSA.

Keywords: cardiac insufficiency; central sleep apnoea; chronic kidney disease; CKD 3; sleep apnoea

Introduction

Sleep apnoea (SA) occurs in 2–4% of the general population [1]. Obesity, male gender, congestive heart failure (CHF), cerebrovascular disease and neurodegenerative disorders are major risk factors for SA. SA syndrome is prominent among the many sequelae affecting chronic dialysis patients, and it is a recognized cause of cardiovascular disease. During episodes of SA, hypoxia triggers brisk sympathetic activation that may result in sympathetic overactivity and hypertension [2]. In chronic dialysis patients, SA frequency has been reported as high as 50% [3]. The reasons for this 10- to 20-fold higher SA prevalence in dialysis patients compared to the general population are not entirely clear. It has been speculated that uraemic toxins, overhydration and comorbidities such as hypertension and CHF may play essential roles [4]. This notion is supported by results from a recent study showing that SA is reversed in renal transplant recipients [5]. In this cross-sectional study, we aimed to test the hypothesis that CKD is more prevalent in patients with SA.

Methods

Study population

In this cross-sectional study, we investigated the prevalence of CKD in consecutive patients referred to standardized full night observed in-hospital polysomnography for suspected SA. All patients referred between January 2004 and April 2007 in whom serum creatinine determinations